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Investigations on the problem of formation and pathophysiological significance of biogenic amines in sublethal radiation injuries.

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Final Technical Report

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Abstract

Basing on the investigations carried out in the 3rd contract year, i.e. during the time from November 1st 1961 to October 31th 1962, our research project

"Investigations on the problem of formation and pathophysiological significance of biogenic amines in sublethal radiation injuries"

has reached the following state:

As a result of 2736 determinations of 7 biogenic amines in urine and blood of rats by means of fluorescence spectrophotometry it has been found, that a single short time total body irradiation of 400, 600 and 800 r leads, according to the dose, to a partly considerable increase of tryptamine, 5-hydroxytryptamine, bufotenine, histamine, 3-hydroxytyramine, noradrenaline and adrenaline. The overexcretion of these amines, which was followed up for 21 and 8 days respectively was to be demonstrated from the first day after irradiation.

Further 736 fluorescence spectrophotometric determinations of amines, carried out in hourly intervals after total body irradiation of the experimental animals showed, that for 5-hydroxytryptamine, histamine, noradrenaline and adrenaline an overexcretion starting from the fourth hour after radiation treatment is to be demonstrated.

By means of further 6928 fluorescence spectrophotometric amine determinations we could show that the measured overexcretion of the above named 7 amines is to be reduced vastly or prevented completely by application of certain inhibitors (phenylacetic acid, alpha-methyldopa); in opposition to other substance tried for radiation protection the named inhibitors have been applied post radiationem.

Functional tests showed, that the amines demonstrated in increased amounts after treatment by irradiation (as well as other amines, demonstrated not yet by us after irradiation treatment) exert - apart from a number of already known effects - a marked influence on capillaries and small vessels, on tissue respiration as well as on change of gas.

Basing on the investigations carried out in the 3rd contract year, i.e. during the time from November 1st 1961 to October 31th 1962, our research project

"Investigations on the problem of formation and pathophysiological significance of biogenic amines in sublethal radiation injuries"

has reached the following state:

- a) By means of 2736 fluorescence spectrophotometric determinations of 7 biogenic amines in urine and blood of rats we could demonstrate, that after a single short time total body irradiation of 400 r follows a marked, after 600 r a stronger and after 800 r an excessive increase of tryptamine, 5-hydroxytryptamine, bufotenine, histamine, 3-hydroxytyramine, noradrenaline and adrenaline. Based on the excretion maxima reached by the single amines adrenaline, noradrenaline and 5-hydroxytryptamine show the highest increase; these are followed by histamine, bufotenine, 3-hydroxytyramine and tryptamine. In these investigations the excretion of amines has been followed up daily, and that for the group of 400 r and 600 r for 21 days, for the group of 800 r for 8 days.

Also in the blood of the irradiated animals partly a considerable increase of the concentration of the amines was to be demonstrated, especially for 5-hydroxytryptamine, histamine and adrenaline.

By "clinical" observation of the irradiated animals one got the impression of a parallelism according to time and degree between the development of the radiation syndrome and the increase of the amines.

- b) In order to clarify the special radiation-biologic question, whether the observed occurrence differing from the norm of biogenic amines is a primary or secondary radiation effect, the above named 7 amines have

been followed up hourly in the urine of the experimental animals after irradiation of 800 r. 736 fluorescence spectrophotometric determinations showed, that for 5-hydroxytryptamine, histamine, noradrenaline and adrenaline an overexcretion is to be demonstrated starting from the 4th hour after irradiation.

- c) By means of 6928 fluorimetric determinations of amines we could show, that the increase of amines, reported under a) is to be highly reduced or completely prevented by intramuscular application of certain inhibitors (alpha-methyldopa 200 mg/kg/day, phenylacetic acid 510 mg/kg/day). In opposition to other substances used for radiation protection the named compounds have been applied post irradiation.

In detail for the two inhibitors the following effect has been observed: phenylacetic acid had in untreated rats no influence on the excretion of catechol amines and indolylalcy l amines worth of mentioning, the excretion of histamine was lowered moderately. In rats treated by whole body irradiation (800 r) phenylacetic acid reduced the considerable increase of biogenic amines reported on under a), and that by reducing noradrenaline and adrenaline moderately up to rather strong, tryptamine, 5-Hydroxytryptamine and bufotenine nearly totally and dopamine and histamine totally. Alpha-methyldopa had in untreated rats no unequivocal effect on the excretion of the indolylalcy l amines and of histamine. It reduced in rats treated by total body irradiation (800 r) the radiation-induced overexcretion of tryptamine, 5-hydroxytryptamine, bufotenine and histamine for nearly 50%. A statement on the influence of alpha-methyldopa on the excretion of catecholamines was not possible up to now, since the fluorescence spectrophotometric determination of the catecholamines after preliminary

application of alpha-methyldopa is disturbed by excretion of the inhibitor as well as by the appearance of methylized metabolites of the catecholamines.

d) In order to clarify the pathophysiological significance of the biogenic amines the following functions tests have been carried out:

- a) change of gas: the measurement of the change of gas was done by means of the KIPF diaferometer. 5-hydroxytryptamine, methylserotonine and bufotenine lower the change of gas of rats, phenylethylamine, tyramine, 3-hydroxytyramine, noradrenaline and adrenaline enhance it. After simultaneous action of indolyl- and phenylalcyamines the lowering effect on the change of gas of the former compounds is predominating.
- b) tissue respiration: the measurement of the tissues respiration was done by means of the WARBURG apparatus and that in liver, kidney, spleen and diaphragma of rats. Tryptamine, 5-hydroxytryptamine, methylserotonine, bufotenine, phenylethylamine, tyramine, 3-hydroxytyramine, noradrenaline, adrenaline, putrescine, cadaverine and iso-butylamine cause a partly considerable lowering of the tissue respiration.
- c) capillaries and small vessels: the judgement on the effect of amines on the capillaries and small vessels was done under microscopical observation of the living object (rat mesotestis preparation) and microfotografical documentation. Phenylethylamine, noradrenaline, adrenaline, tryptamine, 5-hydroxytryptamine, methylserotonine, bufotenine, histamine, isoamylamine, n-butylamine, iso-butylamine, colamine, n-propylamine, dipropylamine and allylamine cause vessel contractions especially in the arterial and arteriolar segment as well as changes of the vessel contents (sludge and stasis phenomena).

For performance of the reported investigations all together 12 persons were employed fulltime. The parties concerned were 4 scientific coworkers, 6 laboratory technicians, 1 animal care taker and 1 washing aid. For the performance of the reported work about 26600 manhours have been expended.